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THE EUROPEAN ASSOCIATION OF NEUROONCOLOGY

### Functional Magnetic Resonance Imaging (fMRI) in Brain Tumour Patients

#### Marion Smits

Abstract: Functional magnetic resonance imaging (fMRI) is increasingly used in the work-up of brain tumour patients preoperatively to assess the relationship between the functionally eloquent cortex and brain pathology. In cases of presumed tumour localisation in or near eloquent brain areas, such as the motor cortex or language areas, fMRI may be advantageous to guide the neurosurgical approach, shorten surgery duration, and obtain prognostic information prior to surgery. For the assessment of the primary motor cortex a good correlation between fMRI and intraoperative electrocortical mapping (ECM) has been reported, with sensitivities and specificities ranging from 88–100 %. For the localisation of language representation areas validation results are controversial with sensitivities from 22–100 % and specificities from 0–100 %, rendering fMRI less suitable as the sole technique for language cortex localisation. For the assessment of hemispheric language lateralisation, however, >90 % agreement between fMRI and the invasive Wada test has led to fMRI now mostly having replaced the Wada test for this indication. There are several limitations of fMRI including issues that are inherent to the technique such as spatial and geometric uncertainty, tumour effects on the fMRI signal, interand intra-individual variability, lack of discrimination between essential and modulating brain regions, and lack of information on the underlying white matter. Such shortcomings need to explicitly be taken into account in every patient. The careful use of fMRI is justified to aid neurosurgical planning but intraoperative ECM remains the gold standard for localising the eloquent brain cortex. **Eur Assoc NeuroOncol Mag 2012; 2 (3): 123–8.** 

Key words: brain neoplasms, magnetic resonance imaging, functional, glioma, brain mapping, motor cortex

#### Introduction

Functional magnetic resonance imaging (fMRI) is increasingly used in the work-up of patients at the preoperative stage to assess the relationship between the functionally eloquent cortex and brain pathology. Inter-individual normal variations of anatomy render such assessment unreliable based on structural imaging alone despite the definition of clear anatomical landmarks [1, 2]. This is even more of an issue when normal anatomy is obscured by a tumour mass effect or when functional anatomy is altered due to cortical plasticity.

fMRI has seen a rapid evolution from its first human application in 1991 [3] to an essential tool in the exploration of human brain function, most prominently in the scientific arena. In 2007, new Current Procedure Terminology (CPT) codes were developed for fMRI by the American Medical Association, signifying the transition of fMRI to a valuable tool in a clinical setting [4].

Recent major advances in clinical fMRI make its acquisition, image processing, and even integration of its findings for neuronavigational purposes relatively easy. However, the technique is not without limitations and validation issues which are easily forgotten when colour activation maps become readily available at the single click of a button. In this paper, the theoretical background, the validity in brain tumour patients, and several considerations of fMRI are addressed.

#### fMRI Background

Blood Oxygenation Level-Dependent (BOLD) fMRI is the most commonly used functional MR neuroimaging tech-

nique. BOLD fMRI takes advantage of the tight link between local neuronal activity and blood flow, called neurovascular coupling [5]. Due to neurovascular coupling, blood flow and volume increase locally with an increase of neuronal activity. This leads to an increase in oxygenated blood that is disproportionate to the increased need of oxygen for neuronal activity. As a result, there is a relative decrease of paramagnetic deoxygenated haemoglobin which in turn leads to an increase of MR signal in those areas of the brain that are active [6]. Such signal changes are small and relative, which means that many measurements need to be made, typically during an alternation of active and baseline conditions in a task that aims to activate the functional brain region of interest. Furthermore, the signal changes occur at a delay after and are more prolonged than the neuronal activity, defined by the hemodynamic response function. A statistical model is created to assess the correlation of the measured signal changes with the task, taking the hemodynamic response function into account. The resulting statistical map is thresholded at a certain p or T value and overlaid in colour on a high-resolution anatomical image which is acquired separately. This is the typical colour "activation" map produced by an fMRI image processing software, which is merely a combination of anatomical and statistical information very indirectly representing neuronal activation.

#### Task-Based fMRI

For clinical application, almost exclusively task-based fMRI is used. During the performance of a task by the subject in the scanner, rapid imaging of the brain is performed. Typically, the entire brain is scanned at intervals of 3-5 s for a duration of about 5 min so that > 100 measurements are made per task. The task consists of active and baseline conditions, which commonly alternate in blocks of 20-40 s. Such so-called blocked paradigms are statistically robust, since a lot of signal is acquired for each condition, but they are restrained because they do not leave much room for unexpected or short stimuli. In an event-related task design, individual stimuli, each representing a specific condition, are presented in random order and rapid succession. Such a task design offers the possibility to present unexpected stimuli as well as many different condi-

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Figure 1. Brain tumour localised in the primary hand motor cortex as evidenced by fMRI activation of a bilateral finger tapping task adjacent to the tumour in the precentral and post-central cortex bilaterally.

tions, rendering it very flexible, but statistically less robust since the signal acquired per condition is generally low. For clinical application, blocked designs are generally well-suited and preferable.

The choice of active and baseline conditions is driven by the brain function of interest. Typical tasks to induce motor activation are finger tapping (Figure 1), wrist flexion, foot tapping, and lip pouting, for somatotopic mapping along the motor cortex. Commonly used tasks to activate the language areas are verb-to-noun generation (Figure 2), passive listening, and picture naming [7]. The baseline condition can simply consist of no activity or stimulus presentation, but may also be used to exclude brain activation associated with the active condition that is not of interest. For instance, in an auditorily presented language task, the presentation of non-language auditory stimuli in the baseline condition will result in language-related activation without activation related to auditory processing in the comparison between active and baseline conditions.

Task-based fMRI is only as good as the patient's ability to perform the given task, since a task that is too difficult will result in underperformance or dropout, resulting in decreased or even absent activation. It is therefore crucial that task difficulty is adapted in patients with neurological and/or cognitive deficits. Training beforehand is also important to ensure adequate task performance; over-learning however should be avoided.

#### Resting-State fMRI (rsfMRI)

A recent development in the scientific field of fMRI is the measurement of spontaneous brain activity, present in multi-



Figure 2. Brain tumour localised in the left temporal lobe of a left-handed patient. fMRI activation of a verb-to-noun generation is present in the expressive language area in the inferior frontal gyrus (arrow), as well as in the receptive language areas in the posterior temporo-parietal cortex (arrowheads). Activation is more pronounce de in the left hemisphere, indicating a left-lateralised hemispheric language representation.

ple networks in the brain, called resting-state fMRI (rsfMRI) [8]. Spontaneous BOLD fluctuations are found to be highly correlated in distinct regions throughout the brain, and are presumed to indicate a functional connectivity within specific and highly organised neuroanatomical networks [9]. In healthy volunteers, such networks can reproducibly be found between the left and right sensorimotor cortices and between language areas, without any task being performed [8]. During an rsfMRI experiment, the subject is instructed to lie in the scanner and think of nothing in particular. Even when subjects are asleep or anaesthetised rsfMRI can be performed, with clear advantages in populations of small children or restless or cognitively impaired patients. The potential advantages for brain tumour patients are obvious: there is no dependency on patient cooperation, on task design or task performance. Several networks can be obtained from the same data set, which can typically be acquired within 10-15 min. A few small studies have recently indicated feasibility of assessing functional connectivity in brain tumour patients, demonstrating a considerable overlap between primary sensorimotor networks assessed with resting state and task-based fMRI [10–12].

In a recent study of 57 brain tumour patients using magnetic encephalography to assess functional connectivity, Martino et al reported a low positive predictive value (64 %) comparing functional connectivity with intraoperative electrocortical mapping (ECM), suggesting that no reliable distinction could be made between critical and less critical eloquent areas [13]. Negative predictive value, however, was high, meaning that in

areas of decreased functional connectivity no active sites were found on ECM and no increase of neurological deficit was found. This would indicate that areas of the brain with decreased functional connectivity are dysfunctional and may be resected without the increased risk of a postoperative neurological deficit. Similar findings were reported by Liu et al [10] and Kokkonen et al [11], demonstrating asymmetrical functional connectivity of the left- and right-hand motor areas in some patients. Task-based fMRI in those patients, however, indicated no hand motor area deficit. Such discrepancy may be explained by white matter infiltration, potentially even occurring at a distance of the primary motor cortex, disrupting inter-hemispheric functional connectivity between the 2 primary motor areas.

Promising as these findings may be, rsfMRI still requires validation in larger patient populations and against an adequate gold standard such as intraoperative electrophysiological cortical mapping (ECM) before its potential application as a clinical tool. Also, image processing tools, at present still largely available in a research environment only, need to be developed that are fast and user-friendly before rsfMRI can be introduced into clinical practice in the same way task-based fMRI was in the last decade. Such developments are certainly not far off, as demonstrated by the recent publication of a tool enabling the interactive assessment of functional connectivity in < 2 minutes for even inexperienced users [14].

#### **Clinical Pre-Surgical fMRI Studies**

The aim of neurosurgery in brain tumour patients is maximum tumour resection, while at the same time minimising the risk of new functional deficits post-operatively. For optimal results, the relationship between the tumour margins and eloquent brain regions needs to be established as accurately as possible. The gold standard for such assessment is intraoperative ECM, which has in fact been shown to significantly modify long-term survival in low-grade glioma patients [15]. However, intraoperative ECM is invasive, requires experience and expertise of the neurosurgical team, increases surgery duration, and requires awake and active participation, collaboration, and motivation of the patient. Additionally, only a limited number of tasks can be tested. Functional MRI may be used to make a risk assessment preoperatively, which is of particular value in young low-grade glioma patients, to plan and guide the neurosurgical approach, shorten surgery duration, and obtain prognostic information prior to surgery [16]. This was demonstrated in an elegant study of 39 brain tumour patients, in 19 of whom treatment plans were altered based on information obtained with fMRI [16]. Most notably, out of 9 patients considered inoperable based on information from conventional imaging, 7 were in fact operated after considering the fMRI results. Similar findings were reported for the pre-surgical assessment of 60 epilepsy patients, in the majority of whom further studies such as the invasive intracarotid amobarbital Wada test were avoided with fMRI and surgical planning was altered in > 40 % [17].

For fMRI to be used in such a setting, both high sensitivity and high specificity are required. High sensitivity for eloquent brain regions is needed to reduce the false negative rate so that no eloquent cortex is missed and no functional deficit is induced by surgery. At high specificity the false positive rate is low, which means that the visualised areas of activation relate to truly eloquent or critical brain regions. At low specificity non-critical brain regions are also visualised, inducing the risk that such areas are avoided at surgery and are subsequently exposed to a less extensive resection than would have been possible.

The validity of fMRI compared with intraoperative ECM as a gold standard has been studied for motor and to a lesser extent for language function representation in the brain.

#### **Motor Function**

Motor cortex assessment has been validated in a multitude of studies that generally report a good correlation between fMRI and intraoperative ECM. Reported sensitivities for localisation of the primary motor cortex range from 88-100 % [18-21]. Specificities are also high, ranging from 87-100 % [18-21]. Such high reliability may be contributed to by the robust activation that is seen with simple motor tasks that can be easily performed by the majority of patients. Also the functional anatomical stability of the sensorimotor area, at both the macroscopic and microscopic levels, probably contributes to the reliability of fMRI of motor function [22]. Spatial accuracy of fMRI motor cortex localisation is found to be within the range of 1-2 cm. Yetkin et al reported that all intraoperative ECM and fMRI sites of activation were within 2 cm, while 87 % were within 1 cm [23]. Importantly though, reliability seems to be decreased with high tumour grades, as demonstrated by Bizzi et al [19]. In their study of 17 patients with benign and malignant brain mass lesions in or near the primary motor cortex, overall sensitivity was 88 %, but only 65 % in grade-IV gliomas. This issue is further addressed in the next section on fMRI considerations.

#### Language Function

In contrast to the high validity shown for fMRI of motor function, results from language function validation studies are controversial, varying from 100 % sensitivity for fMRI to identify all critical language areas to as low as 22 % [24-27]. Reported specificity is even more variable, ranging from 0-100 %. Validation studies of fMRI of language function in brain tumour patients are relatively scarce, are generally performed in small patient populations, and suffer from differences in the validation methods used among the studies, disparities of brain lesions, and the variety of the language tasks performed preoperatively and during intraoperative ECM [22]. The mapping of language function is also more complex than that of the sensorimotor cortex due to the lack of consistent surface landmarks and substantial inter-individual variability. The language cortical network seems to consist of critical regions, essential for language processing, and participating but non-critical areas, which may be resected without inducing a permanent language deficit. These areas cannot be reliably distinguished with fMRI, resulting in low specificity of fMRI compared with intraoperative ECM. In one of only 2 studies in which a site-by-site correlation of fMRI language activation with a large number of tags of intraoperative ECM was performed, the verb generation task was found to be the most sensitive single task out of a language battery of 5 tasks, and is therefore a commonly used task for preoperative lan-



Figure 3. Large high-grade tumour in the left temporal lobe of a right-handed patient. fMRI activation of a verb generation task is present in the expressive-language area in the inferior frontal gyrus (arrows), as well as in the receptive-language areas in the posterior temporo-parietal cortex (arrowheads) in the right hemisphere. No activation is seen in the left hemisphere. Upon surgery, a left-lateralised hemispheric language representation was found with ECM, as would be expected in a right-handed patient. The atypical lateralisation towards the right hemisphere found with fMRI is most likely due to a tumour (mass) effect decreasing the BOLD signal in the affected left hemisphere.

guage fMRI [28]. Bizzi et al used the verb generation task for a site-by-site comparison between fMRI and intraoperative ECM, representing the only validation study in which the same task was used for fMRI and intraoperative ECM [19]. In their study of 17 patients with lesions in or near presumed language representation areas, sensitivity and specificity were found to be 80 % and 78 %, respectively.

Results from studies comparing preoperative fMRI with the Wada test to assess hemispheric language lateralisation, however, are much better [27, 29–32]. With reported agreements of > 90 % in a multitude of studies, fMRI has now mostly replaced the Wada test for the assessment of language lateralisation, given its obvious advantage of being non-invasive and, to a certain extent, giving additional spatial information on the language areas. Care still needs to be taken with large and/or high-grade tumours in or near the presumed language representation areas, since they may interfere with the cerebrovascular hemodynamic auto-regulation that the BOLD response in fMRI depends on (Figure 3) [33, 34]. Such considerations are discussed in more detail in the next section.

Taken together, the results of validation studies do not support the sole use of fMRI to localise language areas, but do show that fMRI can reliably replace the Wada test for the assessment of hemispheric language lateralisation. Atypical language lateralisation demonstrated with fMRI, however, should be considered as an indication for further assessment.

#### **Other Functions**

The visual cortex has been a frequent topic of study since the early days of fMRI, due to its relatively strong BOLD response and easy implementation of stimulus paradigms. Presurgical mapping of the primary visual cortex has been described [20] and may be indicated when the normal anatomy is severely distorted by the tumour and/or when the brain structure of interest is located deep inside the brain and cannot be assessed by ECM [35]. Commonly used stimulus paradigms are flashing lights presented with light-proof goggles and reversing black-and-white checkerboards [35].

Another function that may be assessed with fMRI is visuospatial attention, failure of which results in spatial neglect. This condition arises with damage of the temporoparietal or frontal cortex, the thalamus or the basal ganglia, generally of the right hemisphere [36]. It is an invalidating condition, in which patients behave as if the left part of the world does not exist. Functional localisation may be assessed with fMRI using a line bisection task [36], in which patients are asked to bisect 20-cm horizontal lines, which has been used successfully during ECM [37, 38].

#### Critical Issues

There are several limitations of fMRI that need to be considered when using the technique for pre-surgical assessment of brain tumour patients. These include issues that are inherent to the technique, such as spatial and geometric uncertainty, tumour effects on the BOLD signal, inter- and intra-individual variability, lack of discrimination between essential and modulating brain regions, and lack of information on the underlying white matter [39]. The imaging sequence used for BOLD fMRI is particularly sensitive to postoperative effects, such as metallic implants and surgical staples, air underneath the skull flap, and blood products, as well. This means that additional care needs to be taken in patients who have had previous surgery, biopsy, or haemorrhage. Small regions of haemosiderin deposition may not be visible on conventional imaging, but will show large artefacts in the BOLD fMRI data. Such artefacts are obscured on the fMRI activation colour maps, which would simply show decreased or no activation in the artefactual area. It is therefore crucial that the raw data are scrutinised for such artefacts in every patient [40]. Other issues with pre-surgical fMRI, that may be resolved in the future, are the lack of standardisation of tasks and image processing techniques.

#### **Spatial and Geometric Uncertainty**

Several papers advocate measuring the distance between the eloquent brain region as determined with fMRI and the tumour margin to assess the risk of postoperative neurological deficit. Mueller et al for instance reported that no motor deficit was caused when the distance exceeded 2 cm, but that this risk increased to 33 % when the distance was between 1 and 2 cm, and to 50 % when the distance was < 1 cm [41]. In a more recent study, Krishnan et al suggested that within a 1-cm range intraoperative ECM should be performed while complete resection could be achieved safely when the distance between fMRI activation and tumour margin exceeds 1 cm [42]. The problem with such recommendations is that the measurement of the distance between fMRI activation and brain tumour margin highly depends on the statistical threshold that is applied to the fMRI data after image processing. With a more lenient threshold, the spatial extent of the fMRI activation cluster is increased compared with a more stringent threshold. Due to a large variation of fMRI activation among individuals, which is even more pronounced in brain tumour patients, there is no single optimum statistical threshold that can be used to assess fMRI data [15].

Instead, a centre-of-gravity approach should be used for activation clusters to localise the maximum activation to a certain gyrus. Even with this approach one should keep in mind that fMRI activation is an indirect visualisation of changes in the venous vascular bed near the site of neuronal activity. Small parenchymal venules are estimated to be up to 1.5 mm distant from the site of neuronal activity, while the larger draining veins are maximally 5 mm away [18]. Such spatial uncertainty is inherent to the BOLD fMRI technique, especially at the commonly used MRI scanner field strengths of 1.5T and to a lesser extent 3.0T.

Precise localisation of fMRI activation is further complicated by geometric distortions of the brain that are related to the imaging sequence used for BOLD fMRI, as well as the shift of the brain that occurs upon craniotomy, which may well be up to 2 cm. The latter issue may be resolved by applying intraoperative imaging techniques to update preoperatively acquired fMRI data to the intraoperative situation [43].

**Tumour Interaction with the BOLD fMRI Signal** One of the major issues with the reliability of BOLD fMRI is the fact that the technique relies on the tight link between neuronal activity and hemodynamic changes. Neuronal activity is only measured indirectly as the BOLD signal, which relies on several assumptions of neurovascular coupling. While these assumptions may be valid in healthy volunteers, they may be utterly invalid in the presence of brain or even extra-cranial pathology affecting normal cerebrovascular hemodynamic auto-regulation [44]. Such processes lead to neurovascular uncoupling, which may occur both at the edge of brain tumours as well as in the normal vascular territories at some distance of the tumour. Several studies have shown that fMRI activation may be reduced adjacent to the brain tumour, while neurological function is still intact [33, 45].

At the edge of the tumour, astrocytes and macrophages release nitric oxide which increases local perfusion and may subsequently lead to a decrease of the BOLD signal [33]. Furthermore, high-grade gliomas induce the proliferation of abnormal vessels in the adjacent brain parenchyma that have been shown to lose auto-regulation and have shown a reduced response to physiological stimuli [45]. Both in high- and in low-grade gliomas, neurovascular coupling may be reduced by the tumour's infiltrative nature compromising the neuronal contacts with the capillary beds and astrocytes [33]. Finally, the mass effect of the tumour may have unpredictable effects on the BOLD signal. Moderate compression of the draining



Figure 4. Combined fMRI and DTI tractography in a coronal view of a patient with a tumour near the primary motor cortex. Displacement of both the primary motor cortex (arrows) and the corticospinal tract (arrowheads) is seen.

venules and larger veins may prevent pooling of blood and thus increase the outflow of deoxygenated blood from the area of activation, thereby reducing the BOLD signal [45]. Alternatively, compression of the draining venules may inhibit the outflow and cause pooling of deoxygenated blood in the tumour region, also reducing the BOLD signal [15].

#### White Matter Tracts

Functional MRI provides information on cortical representation of brain function, but not on the course of the subcortical and deep white matter tracts, such as the corticospinal tract (CST) and the arcuate fasciculus for motor and language function, respectively. Inadvertent transection may lead to equally devastating results as resection of the eloquent cortex. Visualisation of such tracts may be obtained with diffusion tensor imaging (DTI) and tractography. Diffusion-weighted imaging provides image contrast sensitive to the diffusion of water molecules [46], which is used in DTI to assess the favoured diffusion direction, such as parallel to highly structured white matter fibres. This information can then be translated into a vector field. When vectors that have the same orientation are combined, the course of white matter tracts may be visualised, which is known as tractography [47]. When fMRI and DTI are combined to perform tractography for specific white matter tracts, displacement and invasion by brain tumours can be visualised preoperatively (Figure 4) [48].

#### Conclusions

Functional MRI is a valuable tool in the pre-surgical assessment of brain tumour patients, but needs to be used with care. Interpretation of the results requires a lot of experience and may be difficult. Knowledge of functional brain anatomy is a first requirement for risk evaluation and to determine which fMRI tasks need to be performed. The shortcomings of fMRI in a clinical setting as described above need to explicitly be taken into account in every patient. In our institution, fMRI, combined with DTI tractography, is used to aid neurosurgical planning but intraoperative ECM is always used for confirmation when activation is shown in the proximity of the brain tumour or if activation is atypical. Most importantly, the absence of fMRI activation does not exclude the presence of functional neuronal tissue, not even within infiltrative tumours.

#### Conflict of Interest

The author states that no conflict of interest exists.

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